

Remarks

Claims 1 and 14 have been amended to remove the exclusion of haematopoietic and lymphatic cells. The amendment is supported by the specification as originally filed. No new matter was added. Claims 1-4, 6-11, and 13-16 remain pending in this application. Reconsideration is respectfully requested in view of the above amendments and following remarks.

Rejection under 35 USC 112, 2nd paragraph

Claims 6, 8, 11, and 13 were rejected under 35 USC 112, 2nd paragraph as being indefinite. Independent claims 1 and 14 have been amended to remove the phrase in question. Applicants assert that the amendment to claims 1 and 14 renders claims 6, 8, 11, and 13 definite. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 112, first paragraph

Claims 1-4, 6-11, and 13-16 were rejected under 35 USC 112, first paragraph as allegedly lacking an enabling specification. Applicants respectfully traverse the rejection. The Examiner stated, "the specification does not teach how to make antibodies and antigen specific of any normal cell that could distinguish one normal cell from another." However, the invention is directed to a method which utilizes antibodies, not to particular antibodies. Antibodies useful for the claimed novel and unobvious method were either known or could be readily obtained by one skilled in the art.

The specification lists several known antibodies useful for the claimed invention. See for example Table 1 at page 9. Many of the antibodies listed would be useful for differentiating between different types of normal cells. For example, using an antibody specific to an integrin labeled with a first fluorescent particle and an antibody specific to thrombospondin receptor (CD36) labeled with a second fluorescent particle would allow one to differentiate between normal cells expressing these antigens. The use of antibodies specific to a particular cell-surface antigen to identify the cells expressing that antigen is such a basic technique for immunohistochemistry and flow cytometry, that Applicants do not understand the Examiner's rejection. Lists of the cell-surface antigens and receptors expressed on various normal cell populations are found in textbooks. Applicants submit that it would be within the skill of the

artisan to select the appropriate antibodies useful for distinguishing between populations of normal cells based on the antigens and/or receptors expressed by those cells. Additionally, the procedures for producing antibodies specific to cell-surface antigens and receptors is very well-known in the art.

MPEP 2164.01 specifically states that a patent should not teach "and preferably omits, what is well known in the art". Applicants submit that methods of making antibodies to antigens found on normal cells is very well known in the art and thus not required to be present in the specification. MPEP 2164.04 quotes the court's decision in *In re Marzocchi*, 439 F.2d 220,224, 169 USPQ 367, 370 (CCPA 1971), stating that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." The Examiner has stated that the specification does not teach how to make antibodies and antigen specific for any normal cells that could distinguish one normal cell from another, but has not provided any reasons why one skilled in the art would not be able to do so. Applicants submit that, on reading the specification, in view of the state of the art at the time of the invention, one skilled in the art would be able to make and use the claimed method commensurate in scope with the present claims. Withdrawal of the rejection is respectfully requested. If this rejection is maintained, Applicants respectfully request a more detailed explanation of why the Examiner believes the skilled artisan would not be able to perform the claimed methods.

With respect to claims 6, 8 and 13, applicants do not understand the rejection. The Examiner stated that the claims lacked enablement because "the specification does not teach how to make antibodies and antigen specific of any normal cell that could distinguish one normal cell from another." However, claims 6, 8 and 13 recite specific antigens. One skilled in the art certainly would have been able to obtain antibodies to such recited antigens without undue experimentation, using standard antibody-producing techniques. Additionally, the specification discloses specific suitable antibodies that bind the recited antigens at page 9 (Table 1).

Rejection under 35 USC 103

Claims 1-4, 6-11, and 13-16 were rejected as allegedly being obvious over Hajek et al. in view of Fodstad et al. and O'Briant et al. Applicants respectfully traverse the rejection.

Combination of the references cited by the Examiner would not have led one to the claimed invention. Hajek et al. teaches the use of flow cytometry. Flow cytometry would not be possible with the claimed method. Flow cytometry as taught by the primary reference could result in signals being quenched and disturbed in such a way that identification of the target cells would be impossible. The presently claimed method is a sensitive method and is capable of detecting only a few target cells within a population of cells. Therefore, the claimed method uses visually detection of, for example, two different target cells by visually recognizing particle bound to the cells.

Fodstad et al. and O'Briant et al., alone or in combination, do not overcome the deficiency of Hajek et al. Combining these references with Hajek et al, which teaches flow cytometry, would not lead one to the claimed invention.

Because combination of the references cited by the Examiner would not have led one to the claimed invention, withdrawal of the rejection is respectfully requested.

Conclusion

With the above amendments and remarks, Applicants believe that the claims now pending in this patent application are in a condition for allowance. Favorable consideration is respectfully requested. If any further questions arise, the Examiner is invited to contact Applicants' representative at the number listed below.

Respectfully submitted,

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| Applicant: | FODSTAD et al. | Examiner: | Davis, M. |
| Serial No.: | 09/331,376 | Group Art Unit: | 1642 |
| Filed: | June 18, 1999 | Docket No.: | 7885.65USWO |
| Title: | METHOD FOR CHARACTERIZATION OF ABNORMAL CELLS | | |

MARKED-UP VERSION TO SHOW CHANGES MADE

In the Claims

Please amend claims 1 and 14 as follows.

1. (Twice Amended) Method to detect and phenotype target cells in cell suspensions by using particles coated with antibodies directed against antigenic determinants/receptors expressed on the target cells, ~~except when the target cells are malignant and normal haematopoietic and lymphatic cells,~~ wherein 2 to 6 antibodies, each conjugated to a particle, wherein the particle is a fluorescent or dyed particle, are incubated under gentle rotation for about 5 minutes to about 2 hours with cell suspensions containing the target cells at 0°C to 25°C, followed by an enrichment procedure, and evaluation of the target cell rosettes microscopically and/or by suitable visualizing or imaging devices, and wherein one antibody is conjugated to one type of particle instrumentally or visually separable by fluorescence, color and size, with sizes of the particles ranging from 0.01µm to 6µm, each antibody of the 2 to 6 antibodies is conjugated to different particles, and the ratio between the number of particles and the number of cells ranges from 0.5 : 1 to 20 : 1 in the cell suspension.

Claim 14. (Twice Amended) Kit to detect and phenotype target cells in cell suspensions by using particles coated with antibodies/ligands directed against antigenic determinants/receptors expressed on the target cells, ~~except when the target cells are malignant and normal haematopoietic and lymphatic cells,~~ wherein 2 to 6 antibodies or ligands each conjugated to a particle, wherein the particle is a fluorescent or dyed particle, are incubated under gentle rotation for 5-10 minutes to 2 hours with cell suspensions containing the target cells at 0°C to 25°C, followed by an enrichment procedure, and evaluation of the target cell rosettes

microscopically and/or by suitable visualizing or imaging devices, wherein the kit comprises particles conjugated to antibodies/ligands, wherein one antibody is conjugated to one type of particle instrumentally or visually separable by fluorescence, color and size, with sizes of the particles ranging from $0.01\mu\text{m}$ to $6\mu\text{m}$, each antibody of the 2 to 6 antibodies is conjugated to the same or different particles, and the ratio between the number of particles and the number of cells ranges from 0, 5 : 1 to 20 : 1 in the cell suspension.